ECHO
Environmental influences on Child Health Outcomes

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NICHD Advisory Council
Today

• Theory (1 slide)
• Goals
• Approach/organization
• Themes
  – Strategic
  – Scientific
• Components
  – What NIH funded (this morning)
• Discussion
Theory

Diagram: Chronic disease risk vs. Life course. The graph illustrates the differences between no/late intervention and timely intervention. Timely intervention results in lower chronic disease risk compared to no/late intervention. The section below the graph highlights plasticity and inadequate response to new challenges.
Goals

• Understand effects of early environmental exposures on child health and development
Goals

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  – Effects: Observation (& intervention)
Goals

• Understand effects of **early** environmental exposures on child health and development
  – Effects: Observation (& intervention)
  – Early: conception to age 5 y
Goals

• Understand effects of early environmental exposures on child health and development
  – Effects: Observation (& intervention)
  – Early: conception to age 5 y
  – Environmental exposures: Society to biology
    • Air pollution
    • Chemicals in our neighborhoods
    • Stress
    • Social networks
    • Behavior—sleep, diet, …
    • Biology—epigenetics, microbiota, …
Goals

• Understand effects of early environmental exposures on **child health and development**
  - Effects: Observation (& intervention)
  - Early: conception to age 5 y
  - Environmental exposures: Society to biology

  – Child health and development
    • High-impact conditions
    • 4 focus areas
      – Pre/peri/post-natal outcomes
      – Upper and lower airway
      – Obesity
      – Neurodevelopment
Approach

• Different from National Children’s Study
• Extant cohorts
  – Individual cohort science
  – Synthetic cohort(s)
• Cooperative agreements
• Focus
ECHO Funding

• $165m per year for 7 years
  – Annual appropriation
  – Exception
    • IDeA States Pediatric Clinical Trials Network
      – Funded for 4 years, up front
Tradeoffs/Challenges

• Alacrity v. patience
  – Need to hit the ground running, but
  – Need time to figure out best practices

• New (NCS) v. existing (ECHO) cohorts
  – No worrying about recruitment, but
  – Challenges in combining existing studies
    • Technical—harmonization
    • Sociocultural—“playing in the same sandbox”

• Many moving parts
  – Integrating IDeA States Pediatric Clinical Trials Network
ECHO Themes
Strategic & Scientific
ECHO Themes
Strategic

- Promote interdisciplinary collaboration so that whole is more than sum of parts.
- Innovations and consensus-building in data harmonization, data sharing
- Rapid cycle program evaluation to improve our program processes and outcomes in real time.
  - ECHO as Learning System
ECHO Themes
Scientific

• Synthetic cohort(s)
  – Whole is greater than sum of parts
    • Conduct solution-oriented observational studies of early environmental origins of common childhood conditions.
    • Combine above and below the skin pathways to pinpoint more precise potential levers of intervention.
    • Employ sophisticated analytic techniques to distinguish modes of intergenerational transmission.
    • Address early origins of child health as well as disease.

• Support infrastructure and training for randomized trials in pediatrics that link to ECHO themes.
Distinguishing modes of transmission critical for intervention design

Conception to age 5: “First 2000 Days”
- Prenatal
- Perinatal
- Early Childhood

Childhood and Adolescence: Reinforcement or resilience
- Mid-Childhood
- Early Teen
- Mid-Teen

Behaviors, e.g., diet, PA, sleep, smoking
Traffic, air pollution, weather, SES, metals, PFAS

Behaviors
Behaviors
Behaviors

Early life programming
Postnatal shared behavior/environment

Cardiometabolic Health
Respiratory Health

Adapted from figure by Emily Oken
Cross-cutting issues

• Heterogeneity
  – Geographic, social, demographic

• Explaining disparities
  – Racial/ethnic, socio-economic

• Replication

• Prevention
  – Primordial prevention
  – Risk stratification, “Precision prevention”
FY16 supplements to FY15 funded centers

[RFP FY17]

One

Data Analysis Center

CHEAR

Genetics Core

PRO Core

Mostly for cohorts

Coordinating Center

Cohort Sites

IDEA States Network

Dozens UG3/UH3

17 Clinical sites & DCOC
• To achieve greatest value for synthetic cohort(s)
  – Cohort hallmarks—quality measures, good retention
  – Maximize
    • Sample size overall and within the 4 focus areas
    • Diversity—race/ethnicity, sex, geography
  – Incorporate
    • Repeated touches early in life course
      – Pre/peri-conception—Moms & Dads
      – Pregnancy—U/S for fetal growth; real-time placenta
      – Infancy—body composition
    • Above/below skin exposures, pathways, covariates
      – From society to biology
    • Microbiome, metagenomics, epigenomics, metabolomics
    • Innovative analytic approaches
• To achieve greatest value for synthetic cohort(s), cont’d
  – Balance
    • Strengths of one-off studies against need to combine/synthesize
    • More mature and newer cohorts
  – Willingness/ability to participate in consortium
  – Overall costs within budget and per-study costs appropriate
• 35 applications funded
  – >35 individual cohorts
  – Institutions in ~38 states/DC/PR
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<tr>
<th></th>
<th>Total</th>
<th>Asian</th>
<th>Black or Af-Am</th>
<th>AI/AN</th>
<th>Cauc.</th>
<th>Multi</th>
<th>Hispanic</th>
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<td>35 Awardees</td>
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<td>Pre/peri/post-natal</td>
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<td>Airways</td>
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<td>Neurodevelopment</td>
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• DAC
  – Create, maintain database and interfaces
  – Develop, conduct sophisticated statistical analyses
    • Data harmonization across disparate cohorts
  – Public data sharing
  – Data security
  – Johns Hopkins Univ/RTI

• CC
  – Policies, communication, coordination, QC
  – Opportunities and Infrastructure Fund
  – Managing biospecimens, biorepository
• IDeA States Pediatric Clinical Trials Research Network
  – Opportunity to enable children in rural and medically underserved locations to participate in clinical research
  – National network for pediatric clinical trials
    • NICHD/NIGMS
    • Support and infrastructure to establishing a teams of highly competent pediatric clinical trial professionals in IDeA states
    • Data Coordination and Operations Center
    • 17 Clinical Sites
• Children's Health Exposure Analysis Resource
  – National Exposure Assessment Laboratory Network—6 sites
  – Data Repository, Analysis, and Science Center
  – Coordinating Center

• Funded in FY15 to serve academic community
• FY16 administrative supplements to support readiness for analyzing ECHO biospecimens
  – NIEHS
<table>
<thead>
<tr>
<th>CHEAR unit</th>
<th>Function</th>
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<tr>
<td>CC</td>
<td>Integrate with ECHO workflow</td>
</tr>
<tr>
<td>DC</td>
<td>Integrate with ECHO data</td>
</tr>
<tr>
<td>WC</td>
<td>Targeted metals, organics</td>
</tr>
<tr>
<td>RTI</td>
<td>Primarily untargeted</td>
</tr>
<tr>
<td>UMN</td>
<td>Tobacco, nutrients</td>
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<tr>
<td>MSSM</td>
<td>Historical exposures (eg teeth)</td>
</tr>
<tr>
<td>Emory</td>
<td>Embed targeted in untargeted</td>
</tr>
<tr>
<td>UMI</td>
<td>Increase # analyses</td>
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• Development and validation of new instruments
• Provide research services and resources to all ECHO Components
  – Psychometric/medical expertise in patient (proxy)-reported measures
• In collaboration with
  – Validation of Pediatric Patient Reported Outcomes in Chronic Diseases (PEPR) Consortium
  – PROMIS, PhenX, Other NIH programs (e.g., Neuro-QOL, NIH Toolbox)
• Northwestern Univ
YOU'RE THE MOST HANDSOME, INTELLIGENT GUY TO EVER COME UP HERE!

YO! OY! OY!
**Epigenomics Flowchart**

**Samples QC**
- Initial Total N
- Total Failed N=
  - Cord blood sample failure
- Total Carried to QC N=
  - Carried to QC
- Total Removed QC N=
  - Replicates
  - Low quality
  - Genotype Mismatch
  - Sex mismatch
- Total Removed QC N=
  - Removed QC
- Total After QC N=
  - After QC
  - After QC

**Probes QC**
- On 450K arrays 485,577
  - Actual SNPs 65
  - On sex chromosome 11,648
  - Non Cg 2,964
  - Quality data (detection 75, Median O.05 439)
  - Total probes after standard QC 470,411

**Normalization with BMIQ**
Include main exposure/outcome of interest in [mode]
Other co-variates may be included in [mode] depending on the analysis
• 102 applications
  – 50 scored
  – Score [min, max; mean] 21, 61; 40
• Recommended applications
  – ECHO WG divided into focus areas for discussion
    • Each focus area group identified top 8-10
      – 26 applications to consider
  – Matt & smaller group married with goals and practices to create tapestry
    • Considered 4 alternate scenarios
    • Discussed with selected IC Directors
    • Final recommendation
      – Added 7 with compelling features to WG-recommended list
      – Total 33 = 31 scored + 2 ND
ECHO Themes

Strategic

• Provide generalizable guideposts/lessons for how to do science in 21st c.
  – Multiple stakeholders
  – Data sharing
  – Harmonization
  – Academic success
  – ECHO as learning system
Strategic

• Incorporate views of multiple stakeholders
  – Congress
  – NIH ICOs
    • ECHO Working Group
  – Investigators
  – Professional Societies
  – Participants, Advocacy Groups
Strategic

• Matching academic success with team science
  – Publication policies
  – Promotion policies?
Strategic

- Move the needle on Data Sharing
  - Among investigators
  - For public use
  - With individual participants
Strategic

• Harmonization
  – Squared-off pegs in rounded-off holes
  – Core elements for cohorts
    • Demographics
    • Typical early health and development
    • Genetic influences on early childhood health and development
    • Environmental factors
    • Patient/Person (parent and child) Reported Outcomes (PROs)
  – Bioinformatics is another area of harmonization
Strategic

- ECHO as learning system
  - Rapid cycle evaluation, Continuous Quality Improvement
  - For early wins and sustained impact
Whole is greater than the sum of the parts

• Questions
  • Solution-oriented

• Design
  • Synthetic cohorts
    • What can everyone agree upon?

• Analysis
  • To match conceptual models
  • Causality in observational studies

Cross-cutting themes
Solution-oriented Questions

• Questions in observational studies that lead to impactful interventions

• Maternal obesity, GWG, GDM
  – Interrelated
  – Interventions to date somewhat disappointing
  – Distinguishing them might lead to more precise interventions
  – Metabolomics could help
Solution-oriented Questions

• Environmental chemicals, air pollution
  – People are generally exposed to mixtures, not single moieties
  – Methodologies needed to examine mixtures
Synthetic Cohorts

• What can everyone agree upon?
  – Something that transcends perinatal, airways, neurodevelopment, obesity/cardiometabolic?
  – Child health rather than disease? (ECHO)
Analytic Methods to Mirror Solution-Oriented Questions

• Exposure mixtures
• Conceptual causal models
  – Intergenerational transmission
    • Biological ("fetal programming")?
    • Socio-cultural, e.g., shared family factors?
ECHO’s Components

FY16 supplements to FY15 funded centers

- Data Analysis Center
- CHEAR
- Genetics Core
- PRO Core
- Coordinating Center
- Cohort Sites
- IDeA States Network

Clinical sites & DCOC
Analytic Methods to Mirror Solution-Oriented Questions

- Exposure mixtures
- Conceptual causal models
  - Intergenerational transmission
    - Biological (“fetal programming”)?
    - Socio-cultural, e.g., shared family factors?
- Trajectories of child health
  - Critical periods
- Shared vulnerability for > 1 outcome
- Unpacking complexity
  - Sophisticated approaches to mediation and time-varying confounding
  - Computational systems science simulation modeling